AN EVALUATION OF THE USE OF RADIATION IN THE TREATMENT OF ENDOMETRIAL CANCER *

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Seventh James Ewing Memorial Lecture

THE opportunity to present the Ewing Memorial Lecture is an occasion for which I am most grateful. It is an honor to address you under those auspices. My appreciation comes also from the fact that Dr. Ewing was one of my teachers. Upon receiving the invitation some months ago, I could not escape the hope that the work to be presented might be of a quality commensurate with the memory of the distinguished gentleman we are honoring. The high esteem in which he is held, however, makes that task extremely difficult. It must be admitted that those first ambitions have not been fulfilled, but perhaps these remarks will serve as an expression of personal appreciation, and as another acknowledgement of his profound influence upon medicine.

James Ewing had more than anatomical interest in cancer. At times he seemed fascinated by the response certain tissues showed to irradiation. His interest in the genesis and clinical behavior of tumors is evident throughout his principal arbeit, "Neoplastic Diseases." In pursuing the study of neoplasms he must have given considerable thought to the physiology and behavior of certain genital epithelia, such as the cyclical alterations occurring in endometrium. The periodic shedding, repair, and reconstruction, as well as the remarkable potential for hypertrophy during gestation, present a striking example of orderly and controlled growth. The close histologic similarity between certain hyperplasias and the more differentiated malignant neoplasms have been of speculative interest in the histogenesis of endometrial cancer. The tendency for

endometriosis to spread, in spite of benignity, parallels the extension of cancer by direct growth and dispersion. It is deemed appropriate, therefore, to select endometrial cancer for discussion here, and in particular the use of preoperative irradiation, which, after a considerable number of years, still presents a rather confused and fluid problem.

The incidence of endometrial cancer reported in most cancer clinics is low in comparison with that for cervical lesions. Some general hospitals, on the other hand, report a more equal distribution. The higher ratio in general hospitals indicates initial clinical symptoms are often attributed to benign causes. Furthermore, the generally accepted concept of endometrial cancer may mitigate against establishing diagnosis before operation, as well as recognizing need to segregate suspected cases into groups for special procedures. With indication for operation, which may be nothing more than excessive bleeding, surgery is performed without loss in time or economy incurred by curettement. If at operation endometrial cancer is found, simple total hysterectomy is considered adequate treatment in the belief that the tumors are slow to spread, and remain for a long while within limits of the myometrium. Risk of dispersion or contamination at operation is believed controlled by closing points of tumor escape through the cervical canal, or through fimbriated ends of fallopian tubes.

The fact that a large percentage of patients present operable lesions favors the generally accepted concept for endometrial cancer. Furthermore, collected statistics for simple total hysterectomy show a five-year survival rate on the order of 65 per cent. The concept fails to take into account, however, any data obtained by preoperative diagnosis that might indicate patients treated inadequately by that procedure. Improvement in clinical results is to be expected if methods of treatment are modified to meet more adequately any individual variations in range and promptness of spread, or in susceptibility to irradiation. Data of that order might best be obtained by exploration of the uterus and removal of tissue for histologic examination. It is to be admitted that preliminary curettage increases cost of patient care and delays definitive treatment. It has also been contended that such a procedure incurs risk of dispersion. It is our opinion, however, that data obtained by curettement are of value that offset any disadvantages. High incidence of correct diagnosis following use of the Randall curette has been reported by Wall.[1] Employed as an office or clinic procedure the problem

in economy and in loss of time is lessened. Positive diagnosis eliminates need for curettement, but that procedure is not omitted if only benign tissue is obtained.

Due to the fact that endometrial lesions are predominantly glandular in type, and present varying degrees of secretory activity, the use of radiation in operable patients may not be considered necessary or practical. Patients treated by irradiation alone are usually those found to be inoperable by extension of tumor, or those with some associated constitutional condition increasing risk of surgery. The frequent association of endometrial cancer with obesity, hypertension, diabetes, advanced age, et cetera, is well known. Those patients present a poorer prognosis, and the lesser results obtained in that group have very likely contributed to the belief that endometrial cancer is not well suited to irradiation. Heyman,[2] on the other hand, obtained among operable patients a five-year survival rate in excess of 60 per cent for treatment by radiation alone. That value resulted directly from advance in technique of radium treatment. Inadequacies of the usual intra-uterine tandem were lessened by packing the uterine cavity with radium tubes introduced individually until all the available space became filled. Other authors have attempted to improve the distribution of radiation by devising hysterostats of different types. Among the older applicators are those devised by Dietel,[3] and the "Y" shaped applicator still in use at the Schmitz clinic in Chicago.[4] Crossen,[5] Friedman,[6] and several others have described special devices.

It is not our intention here to become involved in a comparison of the relative merits of radiation versus surgery in the treatment of endometrial cancer. That question could become more complex than it is today in the management of cervical cancer. In point of fact it is almost impossible to attempt such a comparison for endometrial cancer, due to irregularities in type of clinical material. Several authors have proposed classifications specifying differences in size and extent of tumor. Those depend largely upon examination of the removed uterus, however, and are of little value in clinical examination because pathways of spread for endometrial cancer are not accessible to palpation. Heyman[2] proposed a classification of considerable merit. Patients suited to hysterectomy are termed "clinically operable." Those presenting operable lesions not suited to surgery due to some associated constitutional disorder are grouped "technically operable." The term "inoperable" is applied to

lesions with extension making hysterectomy impractical. Patients pre-
senting downgrowth into the cervix are kept statistically separate in a
group called "corpus et collum."

The Editorial Committee charged with issuing the annual reports
for the League of Nations study of cervical cancer, adopted in 1950
a stage-grouping for use in reporting results obtained in treatment of
endometrial cancer. Emphasis is given the importance of staging based
upon clinical examination prior to treatment, and not influenced by any
findings at operation. The essential data are:

Stage O: Histological findings considered likely to be cancer, but
          inadequate for definite microscopic diagnosis.
Stage I: Tumor is confined to uterus
          (a) Operation advisable
          (b) Bad operative risks
Stage II: Tumor has spread outside the uterus.

The need for a uniform clinical classification to be used in comparing
end results in cancer was emphasized many years ago by Bilroth. Stage-
grouping is as essential in endometrial cancer as it is in cervical cancer.
A substantial percentage of patients fall into Stage Ia. Attempts to im-
prove clinical results by more radical surgery are handicapped by obes-
ity, and the considerable incidence of associated conditions that in-
crease risk of more extensive surgery. In this country, but not so much
abroad, the attempt has been made to improve results by combining
radiation with surgery. Stimulus for that scheme has come chiefly from
the early work of Henry Schmitz,[4] William Healy,[7] and their co-
workers, in which Dr. Ewing had more than an indirect part. Others
pursuing the problem include Scheffey,[8] Payne,[9] Herbert Schmitz,[10]
Corscaden,[11] Miller,[12] Taylor,[13] and McKelvey.[14] In general, the use of
preoperative irradiation has been preferred because a greater tumor dose
is attained by combining intra-uterine radium with external irradiation.

Despite the fact that use of radiation with surgery has not been
particularly satisfactory in cervical cancer, the combined treatment in
endometrial cancer is aimed at meeting more effectively the natural his-
tory of that disease. Nevertheless, the mechanism by which preoperative
irradiation may improve clinical results remains vague. The importance
of degree of differentiation and of uterine size in prognosis has been
debated for different methods of treatment without definite conclusion.
In a recent report by Herbert Schmitz[10] no close relation was noted

between degree of differentiation and prognosis, or with size of uterus. He did, however, find stage of clinical advance a more significant factor in clinical results. His data are among the few that attempt to compare results upon the basis of stage of advance. A point in general agreement is that disappearance, or control of tumor within the uterus, as determined microscopically in the specimen removed after preoperative irradiation is associated with an extremely favorable outlook. Schmitz obtained that result in about three-fourths of his patients, and has for that group a five-year survival in excess of 85 per cent. Similar results have been reported by Taylor and Becker.[13]

McKelvey[14] has lately questioned the usefulness of radiation in the combined treatment. After eliminating the use of x-rays at one period, and of radium at another, he has experienced with increased operability a steady advance in average results for his total series of patients. It is contended that the application of surgery to a greater percentage of patients is responsible for the advance. What part improvement in type of clinical material may have exercised is uncertain. Very properly, however, he criticizes the selectivity that must be exercised in assigning patients for a particular treatment, and attempting to evaluate results upon that basis. In the absence of a generally accepted classification of clinical stage, considerable confusion is to be expected. Furthermore, if a suitable stage-grouping were in general use it is not likely that definite conclusions upon treatment would be established. The respective roles of surgery and radiation are not clearly defined in the treatment of cervical cancer.

Henriksen,[15] Javert,[16] and others have demonstrated for endometrial cancer a tendency toward spread that is greater than generally believed. Lymph node dispersion is important. In addition to the main lymphatic pathways passing lateralward to the regional nodes in the iliac region, it is probable that endometrial cancer may undergo dispersion through ovarian lymphatics connecting with nodes higher in the lumbar chain, as well as through the intimate anastomoses between lymphatics of the uterus and the vagina. Those pathways of spread must be responsible for many therapeutic failures. Control of lymph node metastases by irradiation is highly disputed in cervical cancer. It is not likely that evidence will be forthcoming to show more clearly any effect in endometrial cancer. At the same time improvement in clinical results following preoperative irradiation implies extension of

effective treatment beyond that attained by hysterectomy. Explanation of that question makes important the accumulation of data upon factors responsible for tumor disappearance within the uterus, which, at present, is the most significant prognostic sign in endometrial cancer. It is presumed that preoperative irradiation devitalizes tumor to a degree that lessens risk of spread or contamination at operation. There is general agreement that vaginal irradiation lessens the incidence of vaginal recurrences and metastases. The effects of size of uterus and of degree of differentiation upon prognosis have been difficult to evaluate.

About 1938 we began use of preoperative irradiation at Barnes Hospital, and at the Barnard Free Skin and Cancer Hospital. A course of external roentgen irradiation has initiated the treatment in most instances. In the attempt to avoid intestinal sequelae the amount of irradiation applied to clinically operable patients has been only about two-thirds that generally employed in cervical cancers. Modifications in technique and in dose have been made from time to time in the attempt to increase effectiveness of x-rays, but most of the patients now available for five-year statistics received approximately 1500 r (air) to each of four fields measuring 10 cm. by 15 cm. Patients selected for irradiation alone received about 2400 r (air). Radium is applied near the end of roentgen treatment using one application in clinically operable cases, and two or more in those not to be operated upon. In collaboration with Nolan[17] a method was devised for introducing radium capsules into the uterine cavity that simulates the packing technique described by Heyman.[2] In the earlier years there was considerable variation in length and strength of radium sources, but greater standardization has been attained since 1946.[18] Intravaginal radium was held in place by means of sponge rubber applicators, but more recently we have used modification of the Manchester ovoids, as well as special applicators, devised by Fletcher.[19]

With the aim of evaluating preoperative irradiation we have reviewed the primary cases given definitive treatment during the years 1930-1947 at the Barnard Free Skin and Cancer Hospital and upon the clinic service at the Barnes Hospital. Patients first treated elsewhere, or those given only palliative irradiation, and all private cases have been deleted. Survival rates to be given are relative values. All patients with endometrial cancer are to be included in a more detailed report to be made later by Dr. Sherman.

TABLE I—FIVE-YEAR RESULTS IN 197 PRIMARY CASES OF ENDOMETRIAL
CANCER TREATED AT THE BARNARD FREE SKIN AND CANCER
HOSPITAL AND UPON THE WARD SERVICE OF THE
BARNES HOSPITAL 1930-1947

Treatment	*Classification*	*Five Year Result (Relative)*		
		Number of Patients	*Alive and Well*	*Per Cent*
Irradiation	Technically Operable and Inoperable	94	23	24.5
Irradiation and Hysterectomy	Clinically Operable	60	42	70
Hysterectomy	Clinically Operable	43	29	67.7
Total		197	94	47.7

Operability—52.3 Per cent.   Lost to Follow-Up—10 Per cent.

In Table I, it can be seen that a total of 197 patients are included. Of that number ninety-four were considered inoperable for one reason or another. Hysterectomy, with or without preoperative irradiation, was performed in the remaining 103, presenting an operability rate of 52.3 per cent. For the entire series there is five-year survival free of recurrence of 47.7 per cent. In the group with poor prognosis treated by irradiation alone the value is only 24.5 per cent. For the sixty patients given preoperative irradiation there is a survival rate of 70 per cent, and for hysterectomy alone a value of 67.7 per cent. The difference in results with and without preoperative irradiation in clinically operable patients is of doubtful statistical significance. While the survival rate given for hysterectomy alone is in agreement with that established for that method in collected statistics, any superiority for the combined treatment is not demonstrated in this comparison. Analysis of clinical material might reveal a better prognosis for one group or the other, but those data are not apparent in a table showing total results.

It can be demonstrated that the technique of radium treatment has a determining effect upon results following irradiation. In Table II it can be seen, that, among the ninety-four patients treated by irradiation alone, only 12.5 per cent survived if radium was applied as an intra-uterine tandem, but 30.6 per cent of those given multiple capsules are alive and well at the end of five years. Extending that comparison to the sixty patients given combined treatment, it can be seen that the value for

TABLE II—FIVE-YEAR RESULTS FOLLOWING USE OF INTRA-UTERINE
   TANDEM AND OF MULTIPLE CAPSULES CONTAINING RADIUM IN
      PATIENTS RECEIVING RADIATION ALONE OR IN CONJUNCTION
                    WITH HYSTERECTOMY

Treatment	Radium	Five Year Result		
		Number of Patients	Alive and Well	Per Cent
Irradiation Only	Tandem	32	4	12.5
	Multiple Capsules	62	19	30.6
Irradiation and	Tandem	15	8	53
Hysterectomy	Multiple Capsules	45	34	75.5

intra-uterine radium tandem is 53 per cent, and that for multiple cap-
sules is 75.5 per cent. Explanation of a survival rate for tandem and
hysterectomy falling below that expected for surgery alone cannot be
made except upon the basis of other factors in prognosis. For multiple
capsules, on the other hand, the value of 75 per cent is a ten point im-
provement above the average for surgery alone, and represents an
advance of 10/65, or about 15 per cent. Mention should be made of
the small number of patients in each group. Caution must be used in
making conclusions. In the attempt to evaluate results in such a series,
considerable fluctuation in results is to be expected.

Measurement of 12.0 cm. or more in depth of uterine cavity has
been taken arbitrarily as evidence of enlargement. Analysis of results
according to uterine size is given in Table III. Evidence of extension
outside the uterus was noted at operation in only four patients, three
of whom received preoperative irradiation. Due to the small number of
patients with extension, no attempt has been made to consider the
added effect of uterine size in that group. The marked effect of exten-
sion on prognosis is demonstrated by the fact that only one of the
patients survived the five-year period.

Among patients without demonstrable extension, depth of uterine
cavity was less than 12.0 cm. in sixty-five. Preoperative irradiation was
employed in thirty-two of that number, of whom twenty-eight or 87
per cent survived. The value of hysterectomy alone is 26/33, or 79 per
cent. Larger uteri were found in thirty-four patients. Results after
preoperative irradiation are 13/25, or 52 per cent, and for hysterectomy
alone 3/9, or 33 per cent. Those data are in agreement with earlier

TABLE III—FIVE-YEAR RESULTS IN 103 CLINICALLY OPERABLE PATIENTS
GIVEN PREOPERATIVE IRRADIATION OR TREATED BY
HYSTERECTOMY ALONE

The patients have been divided into groups according to uterine size and extension of tumor outside the uterus.

Depth of Uterine Cavity cm.		Pre-Operative Irradiation			Hysterectomy Only		
		Number of Patients	Alive And Well	Per Cent	Number of Patients	Alive And Well	Per Cent
Less Than 12 cm. No Extension	Tandem	8	7	87			
	Multiple Capsules	24	21	87			
	Total	32	28	87	33	26	79
More Than 12 cm. No Extension	Tandem	6	1	17			
	Multiple Capsules	19	12	63			
	Total	25	13	52	9	3	33
Any Depth With Extension	Tandem	1	0	0			
	Multiple Capsules	2	1	50			
	Total	3	1	33	1	0	0
		60	42	70	43	29	67.7

observations that uterine enlargement affects prognosis adversely. Use of preoperative irradiation resulted in survival better than that following hysterectomy alone. The degree of improvement is found to be greater in patients with enlarged uteri. In that group the technique of radium treatment is important, and improvement in results occurred only in those treated by insertion of multiple capsules. Mention should be made of one other point shown in Table III. It can be seen, that, among the forty-three patients treated by surgery alone, there are thirty-three with uteri less than 12.0 cm. cavity depth. Upon that basis prognosis is expected to be better than for the patients given preoperative irradiation. That factor is of significance in considering the slight degree of improvement in results shown for combined treatment in Table I.

Relation of histology to end results is shown in Table IV. Division is made into differentiated and undifferentiated forms. Incidence of

TABLE IV—FIVE-YEAR RESULTS IN 103 CLINICALLY OPERABLE PATIENTS
THE TUMORS ARE DIVIDED INTO DIFFERENTIATED AND
UNDIFFERENTIATED FORMS

Histological Type	Pre-Operative Irradiation			Hysterectomy Only		
	Number of Patients	Alive And Well	Per Cent	Number of Patients	Alive And Well	Per Cent
Differentiated	38	29	76	27	24	88
Undifferentiated	22	13	59	16	5	31
Total	60	42	70	43	29	67.7

those types is almost identical in the two methods of treatment. Among
differentiated tumors the combined method of treatment resulted in
survival of twenty-nine of the thirty-eight patients, or 76 per cent. The
value for hysterectomy alone is 24/27, or 88 per cent. Preoperative
radiation is not expected to lessen survival rates, but is here not shown
to improve clinical results. The better value for surgery alone may be
due to other factors affecting prognosis, such as uterine size. Among
undifferentiated tumors, however, improvement following preoperative
irradiation appears significant. As can be seen in the table, five-year
survival is found for thirteen of twenty-two patients, or 59 per cent,
but for only five of sixteen patients, or 31 per cent of those treated
by hysterectomy alone.

Disappearance of tumor within the uterus following preoperative
irradiation has been stated to be one of the more significant signs of
favorable prognosis. Factors affecting tumor control are, therefore, of
importance in the attempt to improve clinical results. In this series the
status of tumor after irradiation has been determined by examination of
routine sections made in the diagnostic laboratories. No special search
has been conducted by increasing the number of blocks of tissue taken
from each specimen beyond the needs dictated by adequate microscopic
diagnosis. Data upon the sixty patients given the combined treatment
are shown in Table V. Tumor control is reported in sixty-six per cent.
Histological characteristics have relationship to regression. Control is
found in 70 per cent of differentiated lesions, but in only 60 per cent
of undifferentiated forms. There are, however, other factors that affect
tumor response, such as technique of radium treatment. Those data
are not given in the table. Disappearance of tumor has been noted in

TABLE V—FIVE-YEAR RESULTS IN 60 CLINICALLY OPERABLE PATIENTS
GIVEN THE COMBINED TREATMENT

The patients have been divided into those showing evidence of tumor control within the uterus, and those showing persistent cancer. Results are shown for differentiated and undifferentiated forms.

| Histological Type | Number Treated | Controlled | | | Uncontrolled | | |
		Number of Patients	Alive And Well	Per Cent	Number of Patients	Alive And Well	Per Cent
Differentiated	38	27	24	88.8	11	5	45.5
Undifferentiated	22	13	11	84.6	9	2	22
Total	60	40	35	87	20	7	35

	Total Series	Differentiated	Undifferentiated
Tumor Control Obtained:	40/60—66 Per Cent	27/38—70 Per Cent	13/22—60 Per Cent

three-fourths of patients treated by insertion of multiple capsules, but that effect is noted in less than half the patients treated by intra-uterine tandem. The importance of tumor control is significant. Among the forty patients showing that phenomenon, there is survival of thirty-five, or 87 per cent. Persistent tumor is noted in twenty patients, of whom only seven, or 35 per cent are alive and well. Those results are in close agreement with experience reported by other authors.

Table V includes other data of considerable interest. Among patients with tumor control the survival of differentiated and undifferentiated forms is uniformly good. The respective values are 88.8 per cent, and 84.6 per cent. Similar conditions do not prevail for those with persistent tumor in the uterus. Despite the fact that the number of patients showing residual cancer is so small that results cannot be of more than speculative interest, it should be noted, that, in addition to the overall survival being materially less, a distinct difference is noted for the two histologic groups. Five-year survival in the undifferentiated cases is only half that for the differentiated ones. It should further be noted that tumor control is more difficult to attain for undifferentiated cancers, and occurred in only 60 per cent. Among those treated by insertion of multiple capsules the incidence is somewhat higher. If we consider the 85 per cent survival for those showing tumor control, and add to that number the 20 per cent salvage of those without control, we find the 59 per cent result shown for the combined treatment in Table IV. In a broad sense that indicates a favorable result in about two of three patients for preoperative irradiation, but only in one of three individuals with undifferentiated cancer treated by hysterectomy alone.

Analysis of results in our series of patients does not specifically clarify the confused and fluid problem mentioned in introducing the question of preoperative irradiation for this discussion. The relatively small number of patients falling into the various subdivisions created for study limits conclusions that can be made in a broad statistical sense. In spite of that, however, the experience gained here, combined with that reported by other authors, presents factual data that establish usefulness of preoperative irradiation in the treatment of endometrial cancer. Clinical effects of radiation are best demonstrated in relation to certain characteristics of the natural history of the disease. Prognosis can be predicted in a general fashion, but the result obtained in an individual patient can be evaluated only by observation over a period of time. It is important, therefore, that experience gained in groups of patients be applied in the treatment of each individual.

The most important factor in prognosis for any cancer is stage of clinical advance. Endometrial cancer is no exception. We do not have for stage-grouping a method that approximates the precision attained in cervical cancer. In the selection of clinically operable patients there will be inescapable errors. It is to be admitted that such cases will be few in number. For the series reported here only four of the 103 patients subjected to hysterectomy were found at operation to have extension outside the uterus. Only one of those patients survived a five-year period free of recurrence, and that individual received preoperative irradiation. Operability rate for the entire series is 52.3 per cent. Application of hysterectomy to a higher percentage should incur risk of attempting to treat surgically a higher percentage of patients with extensions.

Among other factors that may affect prognosis is size of the uterus. Explanation of the adverse effect of uterine enlargement can be made only upon a speculative basis. In discarding the four patients noted at surgery to have extension, we found among the remaining ninety-nine, treated with or without preoperative irradiation, that the uterine cavity measured less than 12.0 cm. depth in sixty-five, and more than 12.0 cm. depth in thirty-four. The five-year survival among those with smaller uteri is 83 per cent. Among those with larger specimens it is 47 per cent. Mention should be made of the fact that a uterine cavity of 12.0 cm. depth is not within limits of normal range, but there can be little disagreement that measurements in excess of that length represent en-

largement. We have not demonstrated in our series a significant improvement for preoperative irradiation in the treatment of uteri of the smaller size. A survival rate of 87 per cent was attained in comparison with one of 79 per cent for hysterectomy alone. Method of radium treatment, by intra-uterine tandem or by insertion of multiple capsules, made no difference in clinical results. Among the larger uteri, however, the preoperatively treated patients present a survival of 52 per cent, but only three of the nine patients treated by hysterectomy alone are alive and well. In the group of patients with enlarged uteri the technique of radium treatment is found to have a definite relation to end results. Introduction of radium by multiple capsules resulted in survival of 63 per cent. It cannot be stated that the packing technique for radium treatment is independent of uterine size in so far as end results are concerned, but there is evidence that adequate preoperative irradiation will advance clinical results in patients with enlarged uteri to a level that approaches that obtained in smaller organs. It is probable that the statistical values given above would be modified in one or another direction by adding for consideration the effect of extent of tumor. The series here is inadequate in number for breakdown into smaller categories.

In spite of the indefiniteness some authors have found for effect of tumor differentiation, broad classification of patients here reported into differentiated and undifferentiated forms show definite relation to end results. For the entire group of 103 clinically operable patients there are 65 presenting lesions interpreted as differentiated, and of that number, fifty-three, or 81 per cent are alive and well at the end of five years. For the thirty-eight patients presenting undifferentiated tumors the survival is only eighteen, or 47 per cent. Preoperative irradiation is not demonstrated to improve results among differentiated lesions. The value shown for that method is 29/38, or 76 per cent. For hysterectomy alone the result is 24/27, or 88 per cent. A different circumstance is shown for undifferentiated tumors. With preoperative irradiation the value is 13/22, or 59 per cent, and for surgery alone it is 5/16, or 31 per cent. These results were given before in discussion of Table IV. The total results given in that table fail to demonstrate improvement for preoperative irradiation. That has been the experience of other authors. The question is complex due to the number of factors affecting prognosis, and a much larger number of patients is required for simultaneous

consideration in a total series of all known factors including stage, uterine size, histology, and method of treatment. It was demonstrated earlier that upon the basis of uterine size the group treated by hysterectomy alone presents a better prognosis than those given the combined treatment. Patients treated by hysterectomy alone also presented a better prognosis upon the basis of stage of advance because several individuals had very small lesions discovered unexpectedly after operation for various benign conditions. It is obvious those factors may mitigate against making clearly defined conclusions upon the basis of total results in a series of the number here given. Collection of statistics now being undertaken by the International Committee should be of considerable value.

The most significant factor in prognosis is control of tumor within the uterus. In clinically operable patients data upon that problem can be taken only from those given preoperative irradiation. The study might be extended to groups treated by irradiation alone by performing curettage. As was noted in tables shown above, a total of forty patients were found to show evidence of tumor control. Survival rate for those individuals is 87 per cent. Among the twenty with residual tumor only 35 per cent survived. None of these with persistent cancer would be expected to survive if hysterectomy were omitted. That fact alone establishes surgery as the basic therapeutic procedure. If, however, control of tumor can be gained by preoperative irradiation, then a marked increase in survival rate is to be expected. Average incidence of tumor control, as measured in routine sections made for postoperative diagnosis, is 66 per cent. Method of radium treatment is important. Use of an intra-uterine tandem has resulted in control in less than half the patients treated. Insertion of multiple capsules produces that effect in about three-fourths of the cases. Size of the uterus affects response to irradiation applied by tandem, but the packing technique is largely independent of that factor in as far as tumor disappearance is concerned. Tumor differentiation is of importance. As was noted earlier a 70 per cent control rate was obtained in differentiated forms, but only 60 per cent in undifferentiated varieties. Finally, the amount of radiation reaching the tumor, as well as the period of time over which the application is made, is of determining effect in regression. In the attempt to arrive at an amount of radiation apt to be lethal for endometrial cancer, we have estimated tissue dose in a few more recently treated patients not

included in the series presented here. Expression of dose as an average of 3 points at 1.5 cm. depth to endometrium indicates that more than 7,000 gamma roentgens delivered within a period of about seven days are required for complete regression. That level of dose and intensity has not often been attained in the combined treatment employed during the 1930-1947 period reported here.

In conclusion it can be stated that the natural history of endometrial cancer mitigates against a survival rate in excess of 65 per cent for hysterectomy alone in clinically operable patients. The principal factors known to affect prognosis include stage of advance, size of uterus, and degree of differentiation in the tumor. Prognosis is excellent for early lesions that are well differentiated and occurring in uteri of normal size. If, however, the uterus is enlarged or the tumor undifferentiated, the probability of cure by hysterectomy alone is about one in three. In those instances the use of preoperative irradiation will double the expectancy for survival. The effectiveness of radiation will vary according to dose and intensity. It is apparent that large amounts are required, and administration of that dose necessitates use of x-rays and radium. A more effective distribution of radium radiation is attained by insertion of sources individually to fill all the available space within the uterus. With carefully planned preoperative irradiation one can expect disappearance of tumor within the uterus in about three-fourths of all patients treated. Survival of those individuals is on the order of 85 per cent.

The mechanism by which preoperative irradiation improves clinical results is vague. Much of our present knowledge is based upon observations made by Dr. Ewing. In the absence of full explanation of all phenomena involved, we shall be more successful in treatment if all clinically operable patients are irradiated before surgery is performed rather than select only certain cases for those procedures. It is to be noted, however, that our immediate problems are not so easily solved. Administration of amounts of radiation that appear necessary may result in sequelae that delay operation or increase morbidity. Hysterectomy is the definitive procedure, and it may not be possible to superimpose upon the trauma of surgery the injury accompanying an amount of radiation apt to be lethal for all endometrial cancers. Observations made in conjunction with use of the combined treatment are directly transposable to treatment by irradiation alone in the substantial numbers

of patients not suited to surgery. There is immediate need for greater detail in data upon the effect of clinical stage of advance. General use of a practical stage-grouping for endometrial cancer will facilitate investigations.

Exploration of those confused and rather fluid problems would surely have appealed to Dr. Ewing, and for that reason it is hoped that this presentation will be accepted as another acknowledgement of our appreciation for his life and his work.

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